Cancer Surveillance Series: Recent Trends in Childhood Cancer Incidence and Mortality in the United States

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Background: **Public concern about possible increases in childhood cancer incidence in the United States led us to examine recent incidence and mortality patterns.** ***Methods:*** **Cancers diagnosed in 14 540 children under age 15 years from 1975 through 1995 and reported to nine population-based registries in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program were investigated. Age-adjusted incidence was analyzed according to anatomic site and histologic categories of the International Classification of Childhood Cancer. Age-adjusted U.S. mortality rates were calculated. Trends in rates were evaluated by use of standard regression methods.** ***Results:*** **A modest rise in the incidence of leukemia, the most common childhood cancer, was largely due to an abrupt increase from 1983 to 1984; rates have decreased slightly since 1989. For brain and other central nervous system (CNS) cancers, incidence rose modestly, although statistically significantly (two-sided** $P = .020$**), largely from 1983 through 1986. A few rare childhood cancers demonstrated upward trends (e.g., the 40% of skin cancers designated as dermatofibrosarcomas, adrenal neuroblastomas, and retinoblastomas, the latter two in infants only). In contrast, incidence decreased modestly but statistically significantly for Hodgkin's disease (two-sided** $P = .037$**). Mortality rates declined steadily for all major childhood cancer categories, although less rapidly for brain/CNS cancers.** ***Conclusions:*** **There was no substantial change in incidence for the major pediatric cancers, and rates have remained relatively stable since the mid-1980s. The modest increases that were observed for brain/CNS cancers, leukemia, and infant neuroblastoma were confined to the mid-1980s. The patterns suggest that the increases likely reflected diagnostic improvements or reporting changes. Dramatic declines in childhood cancer mortality represent treatment-related improvements in survival.** **[J Natl Cancer Inst 1999;91:1051–8]**

Partly based on some prior evaluations of temporal trends in childhood cancer incidence *(1–9)*, recent media reports [*(10)*, for example] suggest that incidence is increasing and that the increases may be due to environmental exposures. However, these reports have not generally taken into consideration the timing of changes in childhood cancer rates, recent data from the 1990s, or important developments in the diagnosis and classification of childhood cancers.

Public and governmental concern regarding increasing cancer trends in children stimulated us to examine and provide herein an overview of incidence patterns from 1975 through 1995, based on recently compiled incidence data for 14 540 childhood cancers from several population-based cancer registries. A unique feature of our evaluation is a comparison of the same incidence data categorized by use of the new histology-derived International Classification of Childhood Cancer (ICCC) *(11)* versus the primarily anatomic site-based classification employed by the U.S. registries included in the Surveillance, Epidemiology, and End Results (SEER) Program[1] *(8)*.

METHODS

Since the early 1970s, the National Cancer Institute (NCI) has coordinated the SEER Program, which has collected population-based U.S. cancer incidence data in several metropolitan areas and states *(1,8)*. Although the registries and geographic coverage in the SEER Program have changed somewhat over time, registries in four metropolitan areas (Atlanta, Detroit, San Francisco–Oakland, and Seattle–Puget Sound) and five states (Connecticut, Hawaii, Iowa, New Mexico, and Utah) have reported all cancers newly diagnosed since 1975 among residents in those regions. The nine registries comprise approximately 10% of the U.S. population. Incidence data from 1975 through 1995 were available for this analysis. All primary malignant neoplasms are reportable, excluding the epithelial skin cancers of basal and squamous cell origins.

All neoplasms reported to the SEER Program since 1992 have been coded by use of the International Classification of Diseases for Oncology, Second Edition (ICD-O-2) *(12)*, and those diagnosed prior to 1992 have been recoded to this classification. The ICD-O-2 includes codes for anatomic site (topography) and for histologic type (morphology). In contrast with the predominance of carcinomas among adults, pediatric tumors exhibit substantial histologic and biologic diversity, and most are not of epithelial origin *(13)*. While predominantly anatomic site-based categories are appropriate for adult cancers, a special classification was established for pediatric neoplasms *(14)*, recently updated to incorporate the new codes introduced in ICD-O-2 *(12)*, and designated as the ICCC *(11)*. In preparation for forthcoming NCI and International Agency for Research on Cancer monographs that present childhood cancer incidence data from the United States and around the world, respectively, all pediatric cancers registered in the SEER Program were recently classified according to the ICCC.

Incidence trends for total leukemia, as defined by ICCC category I, were compared with trends for the subtypes of acute lymphoblastic (also designated acute lymphocytic or lymphoid, ICD-O-2 code 9821), acute nonlymphocytic (of which most are acute myeloid leukemia and include ICD-O-2 codes 9840, 9841, 9861, 9864, 9866, 9867, 9891, 9894, and 9910 for erythroleukemia, acute erythremia, acute myeloid, acute aleukemic myeloid, acute promyelocytic, acute myelomonocytic, acute monocytic, aleukemic monocytic, and acute megakaryoblastic leukemias, respectively), and other leukemias (all other ICD-O-2 codes between 9800 and 9941) *(15–18)*. Similarly, incidence trends for all central nervous system (CNS) cancers combined, as defined by ICCC category III, were compared with trends for the histologic groupings of high-grade glioma (9380, 9381, 9401, 9422, 9423, 9430, 9440, 9441, 9442, 9443, 9480, and 9481), low-grade glioma (9382, 9383, 9384, 9400, 9410, 9411, 9420, 9421, and 9424), medulloblastoma occurring both in the cerebellum and in the supratentorial regions (hereafter designated as primitive neuroectodermal tumors or PNET) (9470–9473), ependymoma (9391–9394), oligodendroglioma (9450–9460), and other brain and CNS cancers (9390, 9530, and 9539) *(19,20)*. The histologic categories of glioma, not

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See "Notes" following "References."

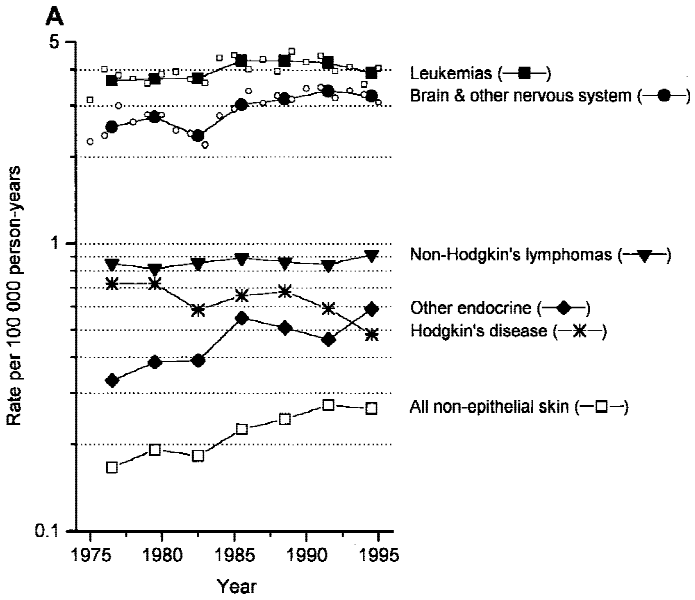
otherwise specified (NOS) (9380), and astrocytoma, NOS (9400), each included many childhood brain tumor cases. Survival of children with glioma, NOS, was evaluated and found to be similar to that of children whose brain tumors were classified as high grade, and survival of children with astrocytoma, NOS, was similar to that of children whose brain tumors were categorized as low grade (unpublished SEER Program data). Because of these similarities in survival, children whose brain tumors were designated as glioma, NOS, were included in the high-grade group and children whose diagnosis was astrocytoma, NOS, were included in the low-grade group.

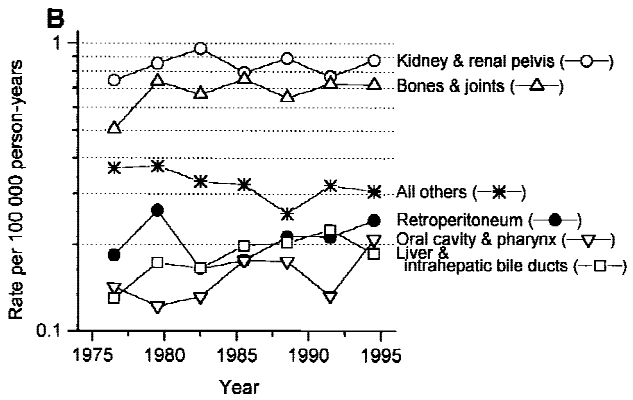
U.S. national death certificate data were provided by the National Center for Health Statistics (Hyattsville, MD) for persons with cancer as the underlying cause of death. Deaths have been coded according to the International Classification of Diseases (ICD), 9th Revision *(21)*. The ICD codes are generally site based, with histology provided for the hematopoietic and lymphoproliferative neoplasms and other cancers to a lesser extent. Annual population estimates used to calculate incidence and mortality rates were provided by the U.S. Bureau of the Census (Suitland, MD).

We calculated rates for seven 3-year time periods from 1975–1977 through 1993–1995 for children diagnosed with cancer or dying of cancer under the age of 15 years, age adjusted by use of 5-year age groups weighted by the 1970 U.S. standard population, expressed per 100 000 person-years. To assess incidence and mortality trends for the two most common childhood cancers (total leukemias and total CNS cancers) in more detail, we calculated age-adjusted rates for single years during 1975 through 1995 in the same population. For each site-based or ICCC major category, the trend in rates from 1975 through 1995 was modeled by use of standard linear regression methods, with the logarithm of the rate as the dependent variable and the midpoint of the calendar year interval as the independent variable *(22)*. We calculated two-sided P values for the standard t test of whether the slope was equal to zero. The data are shown for cancers of 18 anatomic sites (Fig. 1, A–C) and for the 12 major ICCC histologic categories (Fig. 2) for comparative purposes. For clarity, cancer trends for the 18 anatomic sites are shown in three related figures; Fig. 1, A, shows the three most frequent sites (leukemias, brain and other nervous system cancers, and non-Hodgkin's lymphoma) and those with significant increases or decreases, while data for the remaining sites are shown in Fig. 1, B and C. The designations used for the SEER anatomic site and the ICCC histologic classifications differ for a few categories, including brain cancers (designated as brain and other nervous system cancers by the SEER Program and as CNS by the ICCC) and renal cancers (designated as kidney and renal pelvis by SEER and renal by ICCC).

RESULTS

Among the 120 000 new cancers reported by the nine registries each year among persons of all ages (a total of about 1.8 million from 1975 through 1995), approximately 800 were diagnosed annually among children aged 0–14 years, for a total of 14 540 from 1975 through 1995. The distribution of primary childhood cancers is presented in rows for the standard SEER site-based categories (includ-





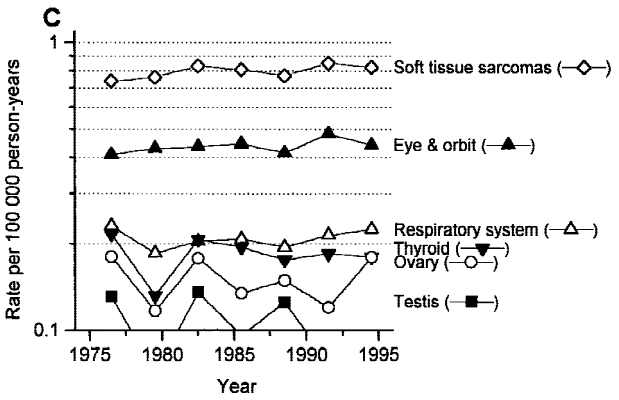


Fig. 1. A) Incidence trends for childhood cancers in nine Surveillance, Epidemiology, and End Results (SEER) Program registries from 1975–1977 through 1993–1995 by use of SEER site recode classifications (3-year rate per 100 000 shown for six site recode categories, including the three most frequently occurring childhood cancers [leukemias, brain and other nervous system cancers, and non-Hodgkin's lymphoma] and those sites with statistically significant increases or decreases [including other endocrine cancers, Hodgkin's disease, and all nonepithelial skin cancers]; 1-year rate per 100 000 shown as **open squares** for leukemias and as **open circles** for brain and other nervous system cancers, the latter two without connecting lines). **B**) Incidence trends for childhood cancers in nine SEER Program registries from 1975–1977 through 1993–1995 by use of SEER site recode classifications (3-year rate per 100 000 shown for six of the 18 site recode categories, including cancers of the kidney and renal pelvis, bones and joints, retroperitoneum, oral cavity and pharynx, liver and intrahepatic bile ducts, and all others combined not shown in Figs. 1, A or C). **C**) Incidence trends for childhood cancers in nine SEER Program registries from 1975–1977 through 1993–1995 by use of SEER site recode classifications (3-year rate per 100 000 shown for six of the 18 site recode categories, including soft tissue sarcomas and cancers of the eye and orbit, respiratory system, thyroid, ovary, and testis).

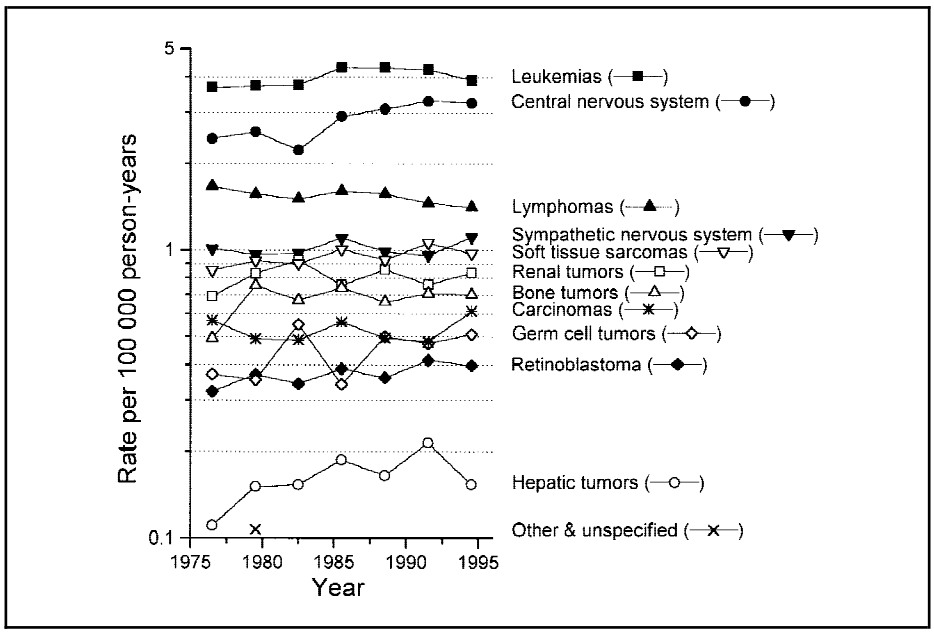


Fig. 2. Incidence trends for childhood cancers in nine Surveillance, Epidemiology, and End Results Program registries from 1975–1977 through 1993–1995 by use of the International Classification of Childhood Cancer (ICCC) *(11)* (results shown for the 12 major ICCC categories).

ing 14 specific anatomic sites and the three major histologic categories of Hodgkin's disease, non-Hodgkin's lymphoma, and the leukemias) and in columns for the 12 major histologic categories designated in the ICCC (Table 1).

The three most frequent major childhood cancers (comprising about 63% of all childhood neoplasms) diagnosed during the 21-year study period were leukemias (30.2% of all cancers diagnosed among children under age 15 years), CNS cancers (21.7%), and lymphomas (10.9%, with 4.4% specified as Hodgkin's disease, 6.2% as non-Hodgkin's lymphoma, and 0.3% as lymphoma, NOS). Next most common were cancers of the kidney and renal pelvis (6.6%), soft tissue (6.1%), and bones and joints (4.7%), with other anatomic sites each accounting for less than 4%.

For seven of the 12 ICCC categories, 97% or more of the cancers in each category were designated by one or two SEER codes. The other five ICCC categories contained cancers at diverse anatomic sites. Cancers of the sympathetic nervous system were almost entirely neuroblastomas that arose in adrenal medulla (34%), soft tissue (21%), retroperitoneum (15%), respiratory system (12%), CNS (8%), or other specified or unspecified sites. Soft tissue sarcomas (of which approximately 50% were rhabdomyosarcomas) arose in a variety of sites; 53% were coded to soft tissue according to the SEER codes, with no other anatomic site exceeding 9%.

Table 1. Distribution of primary malignancies diagnosed among children aged 0–14 years old from 1975 through 1995 in nine SEER* Program registries and classified according to 18 anatomic site categories (rows) and the 12 major histologic categories included in the International Classification of Childhood Cancers (ICCC) (columns)

	Histologic categories of the ICCC												
SEER Program site categories	I, leukemias	II, lymphomas	III, central nervous system	IV, sympathetic nervous system	V, retino-blastoma	VI, renal tumors	VII, hepatic tumors	VIII, bone tumors	IX, soft tissue sarcomas	X, germ cell tumors	XI, carci-nomas	XII, other and unspecified	All ICCC histologic categories
Oral cavity and pharynx	0	0	0	1	0	0	0	2	49	2	103	3	160
Liver and intrahepatic bile ducts	0	0	1	5	0	0	189	0	19	2	0	1	217
Retroperitoneum	0	0	2	185	0	0	0	0	38	12	0	4	241
Respiratory system	0	0	4	149	0	0	0	1	45	14	14	7	234
Bones and joints	0	0	3	0	0	0	0	671	9	0	0	1	684
Soft tissue	0	0	16	251	0	0	0	0	533	63	0	17	880
Skin	0	0	0	0	0	0	0	0	89	0	138	0	227
Ovary	0	0	0	0	0	0	0	0	1	151	0	0	152
Testis	0	0	0	0	0	0	0	0	19	96	0	0	115
Kidney and renal pelvis	0	0	2	25	0	920	0	0	10	2	0	0	959
Eye and orbit	0	0	0	6	443	0	0	0	56	0	9	2	516
Brain and other central nervous system	0	0	2983	92	0	0	0	3	34	41	3	0	3156
Thyroid	0	0	0	0	0	0	0	0	0	1	182	1	184
Other endocrine	0	0	32	411	0	0	0	0	1	55	33	0	532
Hodgkin's disease	0	637	0	0	0	0	0	0	0	0	0	0	637
Non-Hodgkin's lymphomas	0	895	0	0	0	0	0	0	0	0	0	0	895
Leukemias	4396	0	0	0	0	0	0	0	0	0	0	0	4396
Other and unspecified	0	50	5	72	0	0	0	0	108	39	56	25	355
All SEER program site categories	4396	1582	3048	1197	443	920	189	677	1011	478	538	61	14 540

SEER = Surveillance, Epidemiology, and End Results.

Germ cell tumors were largely ovarian or testicular in origin but also occurred elsewhere. The most frequent cancers classified in the ICCC category designated as carcinomas and other epithelial cancers were thyroid and skin cancers (virtually all of which were melanomas). The other and unspecified ICCC category comprised only 0.4% of total childhood cancers.

Fig. 1, A–C, displays incidence trends for the SEER Program anatomic site-based categories from 1975 through 1995, and Fig. 2 shows incidence trends according to ICCC major histologic categories. In the description of the findings shown in these figures, annual percentage increases or decreases are not reported, because such estimates provide adequate summaries only if the trend is relatively linear on the log scale. Few such steady increases or decreases occurred during 1975 through 1995 for the specific childhood cancers shown. As shown in Fig. 1, A, total leukemia incidence rates were stable from 1975 through 1983 but abruptly increased from 3.6 to 4.4 per 100 000 person-years from 1983 to 1984. The increase from 1983 to 1984 was apparent in all nine registries and occurred in both sexes among children in all three 5-year age groups and in both whites and African-Americans (data not shown). During the latter half of the 1980s, rates were stable but then decreased slightly in the early 1990s. The modest increase in total leukemia incidence observed during 1975 through 1995 was not statistically significant.

Brain and other nervous system cancers rose somewhat (from 2.3 to 2.8 per 100 000 person years) from 1975 through 1979 and then decreased to 2.2 in 1983 before increasing to 3.4 in 1986 (Fig. 1, A). Incidence rates were essentially stable after 1986. While the overall increase in incidence for brain and other nervous system cancers from 1975 through 1995 was statistically significant ($P = .020$), most of the increase occurred from 1983 through 1986.

Other childhood cancers were rare, with each characterized by incidence rates lower than 1.0 per 100 000 person-years that often fluctuated from one 3-year period to the next (Fig. 1, A–C). Most pediatric cancers did not significantly increase or decrease in incidence. Hodgkin's disease exhibited a modest but significant decline ($P = .037$), while two rare categories (other endocrine [$P = .012$] and nonepithelial skin [$P = .001$]) showed significant upward trends (Fig. 1, A). Approximately 80% of the endocrine cancers other than thyroid neoplasms were adrenal neuroblastomas. These neuroblastomas exhibited a small increase restricted to infants during the period from 1983 through 1985 (data not shown by single year period). Childhood skin cancers (which exclude the epithelial skin neoplasms of basal and squamous origins) consisted of 60% melanomas and 40% dermatofibrosarcomas, with only the latter accounting for the reported increase in skin cancer.

When the same childhood cancers were classified according to the major histologic categories of the ICCC, the third ranking category (after leukemias and CNS malignancies) was total lymphomas, with incidence rates ranging from 1.7 to 1.5 (Fig. 2). From 1975 through 1995, the incidence of childhood lymphomas declined modestly, although statistically significantly ($P = .027$), due exclusively to a decline in Hodgkin's disease. Other than CNS cancers ($P = .020$), the only ICCC category demonstrating a statistically significant, although small, increase in incidence was retinoblastoma ($P = .030$). Most ICCC categories, however, showed fluctuations in rates typical of rare cancers, with no consistent increase or decrease in incidence. Although the incidence of sympathetic nervous system tumors in the ICCC category changed little from 1975 through 1995, the subset (approximately one third) originating in the adrenal gland (comprising 98% of the 411 neuroblastomas arising in the site-based category designated other endocrine [Table 1]) rose abruptly from 1983 through 1985, but only among infants as noted above.

Fig. 3, A, compares incidence in the geographic areas covered by the SEER Program with total U.S. mortality patterns for childhood leukemias and Fig. 3, B, shows leukemia incidence trends by histologic subtype (SEER Program), while Fig. 3, C and D, shows corresponding data for childhood CNS cancers. Because acute lymphoblastic (designated as lymphoid in Fig. 3, B) leukemia comprises most of total leukemia in children, its incidence pattern resembles that for total leukemia (Fig. 3, B). The incidence of acute lymphoblastic leukemia rose from 2.7 to 3.4 from 1975–1977 through 1987–1989, with most of the increase occurring from 1983 to 1984 (data not shown). Since 1989, the incidence of acute lymphoblastic leukemia has declined slightly to 3.1 for 1993–1995 (Fig. 3, B). Childhood acute myeloid leukemia was uncommon, with no clear trend in incidence. The rates for other and unspecified leukemias were lower than those for acute myeloid leukemia, with an initial decline followed by modest fluctuations. Mortality rates for total childhood leukemia declined dramatically, decreasing from 2.1 to 1.0 from 1975–1977 through 1993–1995 (Fig. 3, A).

Among the total of 657 CNS tumors that we designated as high-grade gliomas, 393 (60%) were gliomas, NOS, with the SEER Program computerized data files lacking information about grade for 90% of these. Of the 1239 CNS tumors that we characterized as low-grade gliomas, 776 (63%) were astrocytomas, NOS, more than one third of which lacked information about grade. The incidence of CNS cancer increased during the mid-1980s for low-grade gliomas, the most common histologic group, as well as for high-grade gliomas and ependymomas (Fig. 3, D). Rates for low-grade gliomas rose slightly (from 0.9 in 1975–1977 to 1.2 in 1978–1980) before declining again and then increased moderately during the 1980s (from 0.9 in 1981–1983 to 1.4 in 1987–1989). Since the late 1980s, rates for low-grade gliomas have remained stable. Rates for both high-grade gliomas and ependymomas rose more rapidly from 1984 through 1989 than low-grade gliomas, peaked in 1990–1992, and then declined. PNET (medulloblastoma) incidence rates changed little over the study period, but these varied according to anatomic site (Fig. 3, D). A modest decline in the rates of PNET arising in the cerebellum was observed, whereas the rates (although based on small numbers) of those occurring outside the cerebellum rose markedly from 1980–1982 through 1993–1995 (data not shown). Oligodendrogliomas and other and unspecified brain tumors were rare, and rates fluctuated over time (Fig. 3, D). In contrast with the dramatic decline in mortality for childhood leukemia, national mortality rates for childhood CNS malignancies decreased modestly, from about 1.0 to just under 0.8 (Fig. 3, C).

Mortality from leukemia and CNS cancers comprised approximately two thirds of total childhood cancer mortality during

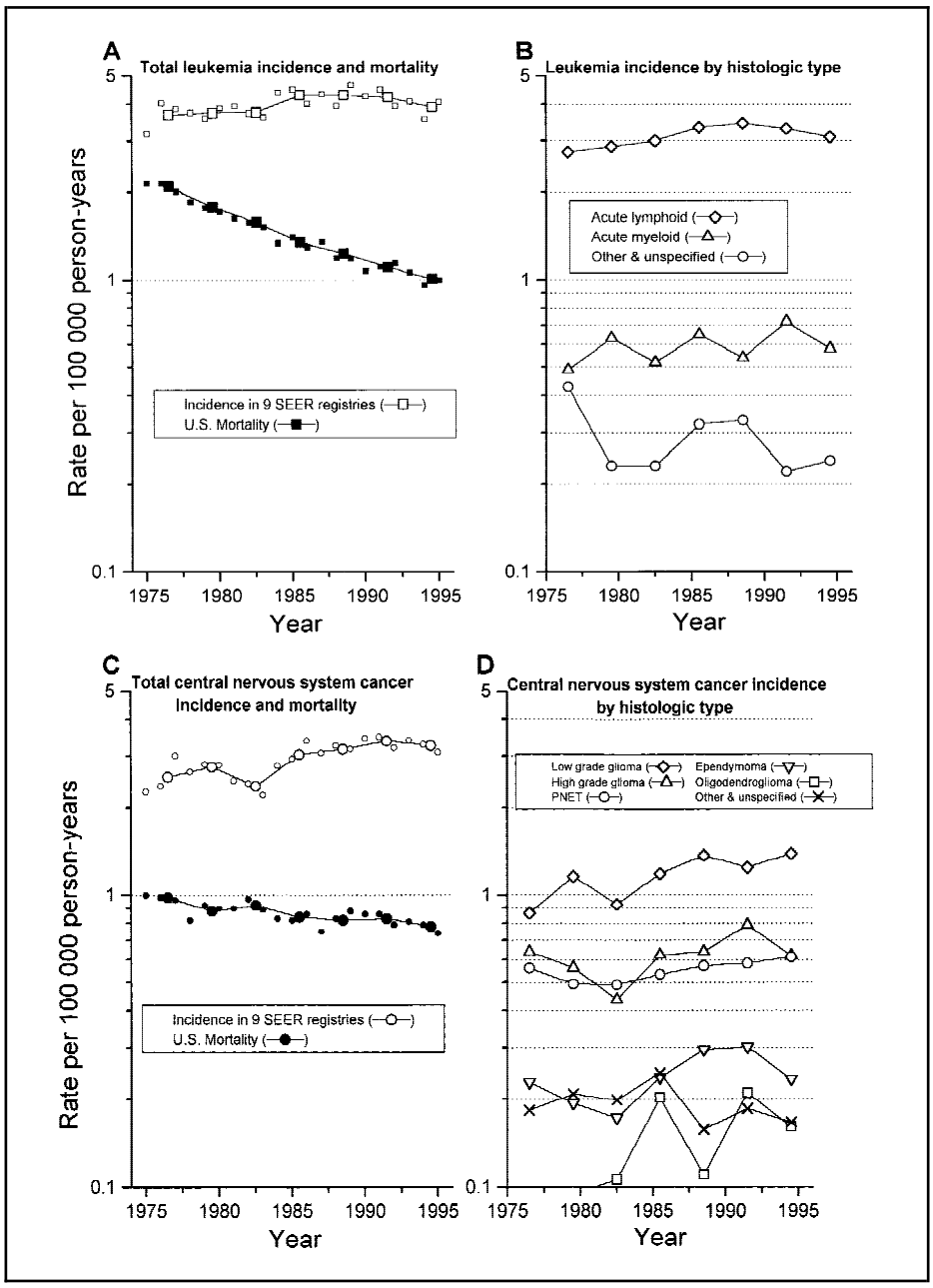


Fig. 3. A) Incidence (in nine Surveillance, Epidemiology, and End Results Program registries) and mortality (entire U.S.) trends for total leukemia in children from 1975–1977 through 1993–1995 (3-year rate per 100 000 shown for incidence and mortality and 1-year rate per 100 000 shown as **open squares** for incidence and **solid squares** for mortality). **B**) Incidence trends for leukemia in children by histologic type in nine SEER Program registries from 1975–1977 through 1993–1995 (results for histologic types of childhood leukemia using definitions of the International Classification of Childhood Cancer (ICCC): Note that categories labeled "acute lymphoid" and "acute myeloid" are designated lymphoid leukemia and acute nonlymphocytic leukemia, respectively, in the ICCC, although the former consists virtually entirely of acute lymphoid subtypes and acute myeloid comprises most of the latter). **C**) Incidence (in nine SEER Program registries) and mortality (entire U.S.) trends for central nervous system tumors in children from 1975–1977 through 1993–1995 (3-year rate per 100 000 shown for incidence and mortality and 1-year rate per 100 000 shown as **open circles** for incidence and **solid circles** for mortality). **D**) Incidence trends for central nervous system tumors in children by histologic type in nine SEER Program registries from 1975–1977 through 1993–1995 (definitions of histologic groupings provided in the "Methods" section). PNET = primitive neuroectodermal tumors.

both 1975–1977 (65%) and 1993–1995 (64%) (data not shown). From 1975–1977 through 1993–1995, total childhood cancer mortality declined 58%. The rates for the leukemias, for CNS cancers, and for all other childhood neoplasms combined decreased 52%, 20%, and 59%, respectively.

DISCUSSION

Our analysis found no large increases or decreases in incidence from 1975 through 1995 for major categories of pediatric cancers in the United States. The slight increase in childhood brain tumors from 1983 through 1986 is consistent with enhancements in diagnostic techniques and changes in classification. Reasons are unknown for the short-term increase in leukemia rates observed from 1983 to 1984.

Investigators evaluating childhood cancer incidence trends have drawn a variety of conclusions, depending on the forms of cancer, the ages of the children, the time periods, and the geographic areas examined as well as the statistical methods used to evaluate changes in rates *(2–8)*. For example, it can be misleading to estimate an overall incidence rate change by the use of differences between the most recent and the earliest years, without considering variations in the entire interval. Other factors may influence the observed patterns, and they include the advent of new diagnostic techniques, such as magnetic resonance imaging *(9,23)*, or the expanding use of an existing diagnostic aid, such as prenatal ultrasound testing *(24)*, the specificity of histopathologic designation or other changes in diagnostic criteria over time *(25)*, and the introduction of a new classification system *(11,14–20)*. Although the SEER Program began reporting in 1973, for geographic comparability our analysis used data from 1975, since two of the nine oldest SEER registries first joined in 1974 and 1975, respectively. The rarity of most childhood cancers *(7,26,27)* adds to the difficulty of evaluating trend patterns, even with 21 years of data from the large geographic areas included in the nine SEER registries. Comparison of U.S. with international incidence trends can be difficult and potentially misleading because of the methodologic problems described above and because of differences in population census quality, completeness and accuracy of childhood cancer ascertainment, and differences in coding and classification *(27–30)*.

Overall, the increases and decreases in incidence for specific types of the leukemias were modest, restricted to acute lymphoblastic leukemia, and confined to short intervals within the study period. The abrupt increase for total leukemia and for acute lymphoblastic leukemia from 1983 to 1984 is consistent with a step

function (e.g., jump model), with a lower rate before 1984, followed by an abrupt rise and a higher rate subsequently, and was seen in all nine SEER registries and among all subgroups defined by sex, age, and race. This pattern could be consistent with changes in diagnostic procedures or leukemia classification, but we are unaware of any such changes preceding the abrupt increase that occurred in childhood leukemia (and, more specifically, acute lymphoblastic leukemia) in the geographic regions covered by the nine longstanding SEER registries. Minor fluctuations were seen from 1975–1977 through 1993–1995 for acute myeloid leukemia. In parallel with the initial rise in acute lymphoblastic leukemia in the mid-to-late 1970s, the incidence of other and unspecified leukemias declined from 1975–1977 through 1978–1980, consistent with a shift in histopathologic classification. Specifically, the introduction and expanded use of selective chemotherapy agents and immunophenotyping in the late 1970s probably contributed to improvements in specification by cell type, resulting in the decline in other and unspecified leukemias in the United States *(7,25)*. Consistent with the trends for total leukemia observed in the SEER registries from 1975 through 1995, incidence also changed little in the Greater Delaware Valley region from 1970 through 1989 *(6)*. Moreover, there was no increase in total childhood leukemia incidence over the longer term based on limited incidence data for white children from five geographic areas (Atlanta, Connecticut, Detroit, Iowa, and San Francisco–Oakland) for 1947–1950, 1969–1971, and from 1975 through 1995 [*(3);* unpublished SEER Program data].

As shown previously by Smith et al. *(9)* by use of SEER data, the incidence pattern of increasing rates for childhood CNS cancers is also consistent with a step function, with a lower rate prior to 1984, followed by an abrupt rise, mostly due to increases in cancer of the brain stem and cerebrum, and then a constant higher rate afterward. Smith and colleagues conjectured that the timing and pattern of the rapid increase in the mid-1980s, seen for microscopically confirmed low-grade gliomas of the brain stem as well as for low-grade and high-grade gliomas of the cerebrum and for ependymomas, paralleled the advent and dramatic expansion of magnetic resonance imaging in the United States and the introduction of stereotactic biopsy *(9,23,31)*. Our evaluation of childhood glioma trends according to grade should be interpreted cautiously, since large proportions of patients with these CNS cancers lacked sufficiently detailed characterization of their gliomas to validate the designation as "high-grade" or "low-grade" gliomas. Publication of a proposed classification revision by Rorke et al. *(19)* in 1985 may have further contributed to the abrupt increase in CNS incidence in the mid-1980s by reducing the proportion of slow-growing, low-grade gliomas previously designated as "benign" and thus not registered by the SEER Program. Our interpretation is further supported by the absence of an increase in childhood CNS mortality from 1983 through 1986 that should have occurred if incidence was truly increasing, since there was little concomitant advance in the efficacy of treatments for most types of childhood CNS neoplasms. Elsewhere in the United States, overall CNS tumor incidence rose significantly from 1970 through 1989 in the geographic region covered by the Greater Delaware Valley Pediatric Tumor Registry *(6)*. Although the published data provide annual incidence rates for CNS tumor subcategories only and not all childhood CNS cancers combined, additional analysis of the total childhood CNS neoplasms (unpublished Greater Delaware Valley Pediatric Tumor Registry data) suggests that the incidence trends were consistent with the pattern in the geographic areas covered by the nine longstanding SEER Program registries during the same time period.

For other SEER site categories, statistically significant changes were limited to less common tumors. An increase in adrenal neuroblastomas, restricted to infants during a narrow time frame (from 1983 through 1985), accounted for virtually all of the rise in incidence of nonthyroid endocrine tumors. The timing of the increase is coincidental with the widespread diffusion of prenatal ultrasound testing *(24)*, which was not performed for neuroblastoma screening but was able to detect adrenal masses as incidental findings *(32,33)*. In contrast with the incidental detection of adrenal neuroblastomas in the United States, widespread screening for these tumors has been carried out in Canada *(34)* and Japan *(35)*, two countries in which increases in adrenal neuroblastomas were observed among infants. The subsequent stabilization of adrenal neuroblastoma rates at a higher level may represent near saturation of the U.S. population with prenatal testing. This interpretation is also supported by the growing number of clinical reports of prenatally diagnosed adrenal neuroblastomas *(36)*, some of which regress or spontaneously mature to benign pathology *(37–39)*.

Although malignant melanomas represent the largest category of childhood skin tumors, incidence rates in children remained stable during the study period, in contrast with the notable increases spanning decades among white adults *(40)*. The small increase in childhood skin tumors was due to dermatofibrosarcomas, a type of deep-dermis tumor related to giant cell fibroblastomas, often associated with recombination between chromosomes 17 and 22 and more common in adults than in children *(41,42)*. While the rise in dermatofibrosarcomas may result from increasing specification of childhood sarcoma by anatomic site and from advances in molecular techniques, further evaluation is limited by small numbers of cases (representing <9% of total childhood sarcomas).

The small decrease in childhood Hodgkin's disease is consistent with a similar decline in Hodgkin's disease among adults in the United States and other countries due in part to diagnostic shifts, with a corresponding increase in the diagnosis of non-Hodgkin's lymphoma since the 1970s *(43–46)*. In contrast to the long-term increase in incidence for non-Hodgkin's lymphoma among adults *(44)*, there has been little variation in this trend among U.S. children, suggesting that improvements in classification cannot entirely explain the decline in childhood Hodgkin's disease. Similarly, the occurrence subsequent to 1989 of the greatest rate of decline for childhood Hodgkin's disease in parallel with a decline for childhood acute lymphoblastic leukemia is also inconsistent with misclassification between these two disorders.

Most ICCC histologic categories of childhood tumors occur in only one or two anatomic sites. In fact, for 70% of cancers among children under age 15 years (e.g., those in ICCC categories I–III and V–VIII), 97% of the tumors in each category were localized to one or two sites. Thus, trends would be similar regardless of whether SEER or ICCC categories are used. However, for other tumor types, the ICCC categories group cancer cases in a histologically more

meaningful manner. The greatest differences between the SEER site and ICCC histologic categories were apparent for sympathetic nervous system cancers, which include tumors ranging from the undifferentiated neuroblastomas to the fully differentiated ganglioneuroblastomas, all believed to derive from primordial neural-crest cells *(39)*. Sympathetic nervous system tumors, germ cell tumors, and soft tissue sarcomas arise in a variety of widely dispersed anatomic sites, so analysis of trends in these ICCC categories leads to insights not possible from evaluation by anatomic site. In the absence of a clear understanding of the etiology of most childhood cancers, however, it may be useful to continue to evaluate descriptive findings by both ICCC and site categories.

For ICCC histologic categories, retinoblastoma displayed a clear trend, with a statistically significant but modest increase, primarily confined to infants. Although there was no change overall in incidence of retinoblastoma reported from the Greater Delaware Valley Pediatric Tumor Registry from 1970 through 1989, a nonsignificant increase was seen among infants in conjunction with a significant decline among children aged 1–2 years *(6)*. Similarly, the incidence of retinoblastoma rose among infants with unilateral disease in Great Britain from 1962 through 1991 as incidence declined among children aged 1–2 years *(28)*. While the patterns in the Greater Delaware Valley and Britain have been ascribed to shifts toward earlier age at diagnosis, this explanation cannot fully account for the overall increase observed in the regions covered by the SEER registries.

For childhood cancer mortality, there were substantial declines in the study period. The reduction was greater than 50% for leukemia mortality, with improvements also observed for other cancer sites, although to a lesser extent for CNS tumors *(8,9)*. The dramatic decrease in mortality observed for childhood leukemias, described in more detail elsewhere *(3)*, is consistent with treatment-based improvements in survival, particularly for patients with acute lymphoblastic leukemia *(5)*. In contrast, the modest improvement in mortality for childhood CNS tumors during 1975–1995 suggests only limited progress in therapy for those cancers. Striking improvements in survival have been reported for childhood renal cancers (mostly Wilms' tumor), retinoblastoma, lymphomas, and, to a lesser extent, other cancers since the start of the SEER Program in 1973 *(5,8)*.

In summary, there were no consistent large increases or decreases in incidence for the major categories of cancer among children aged 0–14 years during 1975 through 1995, based on data from the nine longstanding registries in the SEER Program. The modest increases for childhood CNS cancers, leukemias, and infant neuroblastomas were confined to short intervals in the mid-1980s. This pattern suggests that the increases likely reflected reporting or diagnostic changes rather than effects of environmental influences. The short-term jump in CNS tumors in the geographic areas covered by the SEER Program registries has been ascribed to preceding developments in diagnostic technology, new neurosurgical procedures, and classification changes *(9)*. However, it is not apparent what specific diagnostic, reporting, or classification changes account for the abrupt jump from 1983 to 1984 in leukemia rates or the increase during the mid-1980s for adrenal neuroblastomas. Reasons for the modest continuous increases in dermatofibrosarcomas and retinoblastomas (both rare) and the small declines in Hodgkin's disease during the interval 1975 through 1995 are also not entirely clear. However, the dramatic declines in mortality for many childhood cancers represent treatment-related improvements in survival. Childhood cancer trends in the United States should continue to be monitored, and postulated risk factors (including environmental exposures) should be evaluated to identify the causes of cancers in children.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically to the NCI on a biannual basis, and the NCI makes the data available for analysis.

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